

## REVIEW

# Interaction among inflammasome, autophagy and non-coding RNAs: new horizons for drug

Qinqin Pu<sup>1,2</sup>, Ping Lin<sup>1</sup>, Zhihan Wang<sup>3</sup>, Pan Gao<sup>2</sup>, Shugang Qin<sup>2</sup>, Luqing Cui<sup>1</sup> and Min Wu<sup>1,\*</sup>

<sup>1</sup>Department of Biomedical Sciences, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND 58203, USA; <sup>2</sup>State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China; <sup>3</sup>West China School of Basic Medical Sciences & Forensic Medicine, Sichuan University, Chengdu 610041, China

\*Correspondence: Min Wu, min.wu@und.edu

## Abstract

Autophagy and inflammasomes are shown to interact in various situations including infectious disease, cancer, diabetes and neurodegeneration. Since multiple layers of molecular regulators contribute to the interplay between autophagy and inflammasome activation, the detail of such interplay remains largely unknown. Non-coding RNAs (ncRNAs), which have been implicated in regulating an expanding list of cellular processes including immune defense against pathogens and inflammatory response in cancer and metabolic diseases, may join in the crosstalk between inflammasomes and autophagy in physiological or disease conditions. In this review, we summarize the latest research on the interlink among ncRNAs, inflammasomes and autophagy and discuss the emerging role of these three in multiple signaling transduction pathways involved in clinical conditions. By analyzing these intriguing interconnections, we hope to unveil the mechanism inter-regulating these multiple processes and ultimately discover potential drug targets for some refractory diseases.

**Key words:** ncRNAs; innate and adaptive immunity; inflammasome; autophagy; precision medicine

## Introduction

Autophagy (self-eating), first described by Ashford and Porter in 1962<sup>1</sup>, is a ubiquitous eukaryotic cellular process to provide the metabolic needs and the renewal of some organelles. The important step of autophagy (macroautophagy) process is the formation of autophagosome, which needs the preinitiation complex to activate the Class III PI3K complex (Bcln1, ATG14L, VPS34 and VPS15), and generate PI3P at the site of nucleation of the isolation membrane, finally

forming the phagophore<sup>2</sup>. Then an elongation reaction enlarges with phosphatidylethanolamine-conjugated LC3 until forming an autophagosome. Lysosome then fuses with autophagosome and degrades cargoes. Chaperone-mediated autophagy can select cargoes with specific target sequences to lysosome. Thus, autophagy can be classified as selective and nonselective ones. The selective process can specifically remove protein aggregates (aggrephagy), organelles such as peroxisomes

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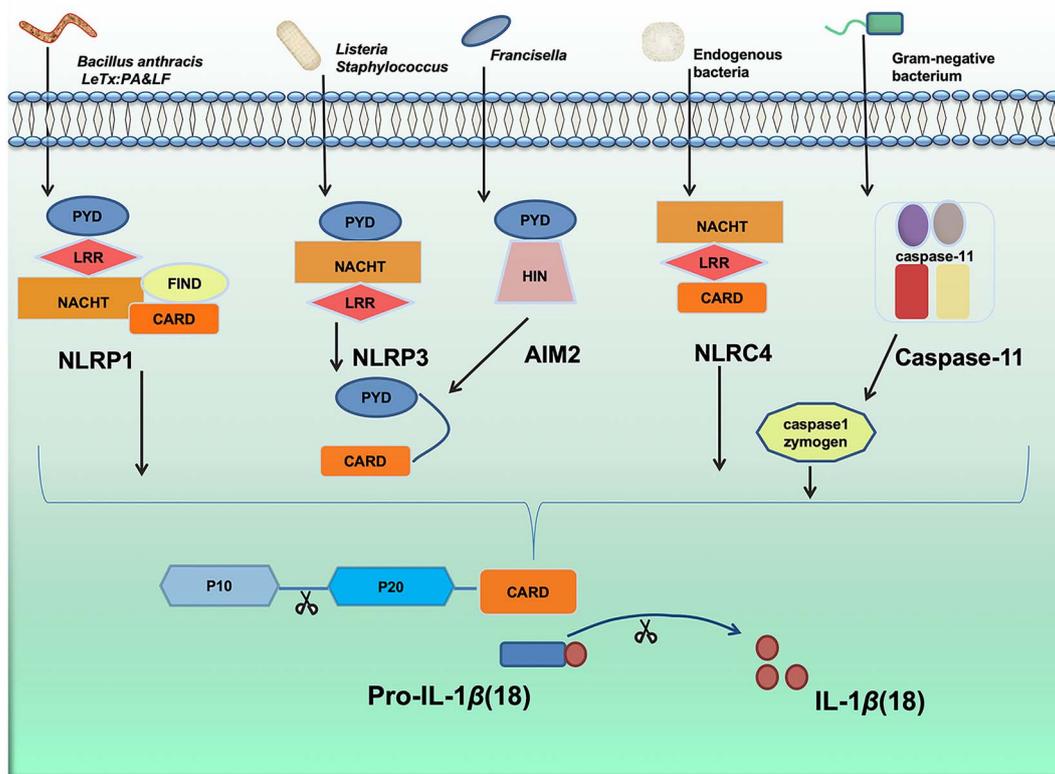
(pexophagy), mitochondria (mitophagy), endoplasmic reticulum (reticulophagy), ribosomes (ribophagy), lipids (lipophagy) and bacteria (xenophagy). Growing evidence indicates that autophagy plays a key part in a broad scope of cellular functions including metabolism, inflammation, and immunity<sup>3,4</sup>, but the actual role and underlying mechanism of autophagy in the physiological and pathological processes remains incompletely understood.

As a barrier to bacterial infection, the autophagic pathway has multiple functions, such as the degradation of macromolecules<sup>5</sup>, an alternative source of anabolic nutrients under starvation<sup>6</sup>, and the degradation of intracellular pathogens as a means against infection<sup>7</sup>. On the other hand, certain bacteria, such as *Pseudotuberculosis*<sup>8</sup>, *Yersinia pestis*<sup>9</sup> and *Chlamydia trachomatis*,<sup>10</sup> can survive and thrive by taking advantage of the autophagy machinery to evade the host defense<sup>11</sup>. But it is evident that autophagy can be modulated to enable an effective immune response. Therefore, autophagy may serve as an auxiliary control measure for some infectious diseases but may not work for infections of other microorganisms. Moreover, autophagy has a similar complex role in cancer and metabolic diseases<sup>12</sup>, thus of great impact on human life. We strongly believe that further dissecting the mechanisms of the survival or death of pathogens in autophagic conditions should lead to better strategies for effective treatment of different diseases especially infectious diseases.

By crosstalk with autophagy, inflammasomes influence the effector cells of innate and adaptive immunity during inflammatory response<sup>13</sup>. Inflammasome recognizes pathogens like bacteria and damage-associated molecular pattern components via specific receptors, such as NOD-like receptors (NLRs) (Fig. 1)<sup>14</sup>. Classic inflammasomes including NLRP1, NLRP3, NLRP4 and AIM2 inflammasomes directly or indirectly activate caspase-1, resulting in a highly inflammatory form of programmed cell death (pyroptosis) and facilitating maturation of IL-1 $\beta$  and IL-18<sup>3,15-17</sup>. Among them, NLRP1 is relatively unique in the family of NLRs containing FIIND (function-to-find domain) domain and CARD (caspase activation and recruitment domain) domain at the C-terminus of the protein. NLRP1 was earlier reported to be activated by hydrolysis of the lethal factor (LF) of *Bacillus anthracis* and the mechanisms were recently characterized<sup>15</sup>. Vance *et al.* uncovered that LF could hydrolyze the N-terminal peptide of NLRP1 to produce a new N-terminus. This new N-terminus promotes the degradation of NLRP1 via the N-end rule proteasomal degradation pathway, while the FIIND domain is hydrolyzed by proteasomal degradation and forms a CARD domain at the C-terminus (984aa-1233aa), thereby completing inflammasome assembly and activation processes<sup>16</sup>. Up to date, NLRP3 appears to be the most well studied inflammasome. As an important component of innate immunity, NLRP3 plays an important role in both immune response

and a variety of disease processes<sup>17</sup>, including Type 2 diabetes<sup>18</sup>, Alzheimer's Disease<sup>19</sup>, and atherosclerosis<sup>20</sup>. Therefore, as the core of the inflammatory response, NLRP3 inflammasome studies may indicate new targets for the treatment of various inflammatory diseases. Due to the diversity of NLRP3 agonists, the specific mechanism of action and signal axis of agonist-receptor proteins remain to be fully understood. Different from NLRP3 and other NLRs, the NLRP4 inflammasome does not contain PYD domain, whereas its CARD domain directly binds with Caspase 1 to coordinate complex assembly. The function of NLRP4 is closely associated with the NAIP protein (NLR family apoptosis inhibitory protein), which can bind to flagellin and type III secretion apparatus and other bacterial structural components<sup>20,21</sup>. Mechanistically, the NAIP protein uses a catalytic surface that is highly similar to the NLRP4 protein to initiate a "self-replication" activation process of the NLRP4 protein, and avoiding recognition of the NAIP's own surface ensures the specific activation for NLRP4 inflammasome<sup>21</sup>. AIM2 inflammasome is characterized as a DNA inflammasome by its ability to detect foreign dsDNA including viral dsDNA, bacterial dsDNA and even broken host dsDNA and mitochondria DNA<sup>22</sup>. Hence, AIM2 inflammasome is a very important intracytoplasmic sensor, which is involved in infection and autoimmune disease. Although there is evidence indicating that NLRP2, 6, 7, 12 and IFI16 inflammasomes can also form inflammasome complexes, their specific physiological functions require further details<sup>3</sup>. Unlike classic inflammasome, non-classic inflammasome caspase-11 senses bacterial lipopolysaccharide (LPS) and also regulates IL-1 $\beta$  and IL-18 expression<sup>17</sup>. The overexpressed IL-1 $\beta$  and IL-18 then accelerate the deterioration of inflammation factors. On the contrary, some pathogen-associated proteins produced after infection can inhibit the formation and activation of inflammasome leading to the decay of IL-1 $\beta$  and IL-18, which may hamper pathogen eradication and trigger chronic infection or result in cell death<sup>23</sup>. Therefore, an alternative approach to clearing the pathogens, such as autophagy, may serve as a compensatory mechanism to strengthen host defense by modulating inflammasome-driven responses.

A non-coding RNA (ncRNA) refers to an RNA that does not encode a protein, which are often classified into different categories based on the length: transfer RNAs and ribosomal RNA, small RNA [microRNA (miRNA) and siRNA (small interfering RNA)]<sup>24</sup>, piRNA (Piwi-interacting RNA), small nucleolar RNAs (snoRNA), nuclear RNAs (snRNAs), repeat associated small interfering RNAs (scRNAs), circular RNA (circRNA), long intergenic noncoding RNA (lincRNA) and long noncoding RNA (lncRNA)<sup>25-28</sup>. A regulatory RNA primarily exercises its biological function at post transcription levels. Approximately 75% of the human genome can be transcribed into RNAs, but 74% of which are not translated into proteins<sup>29</sup>. ncRNAs play an important role in many



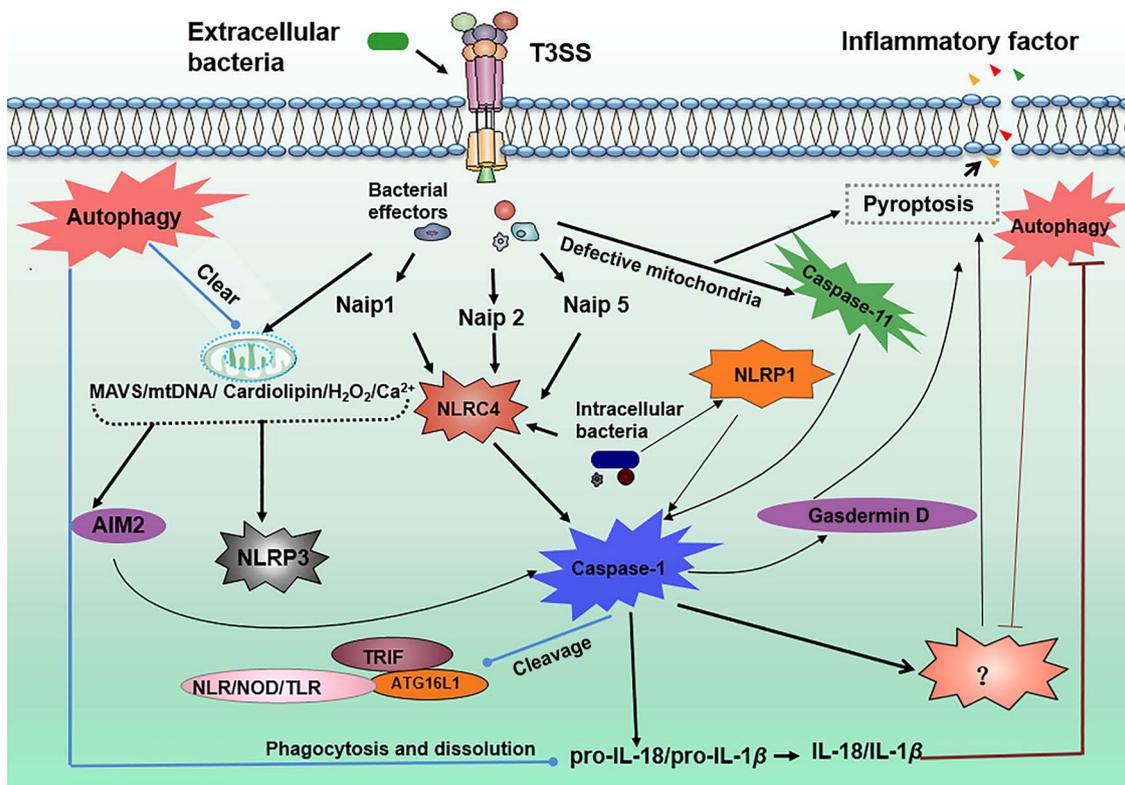
**Figure 1.** The process of bacteria activating inflammasomes. Different bacteria activate different inflammasomes. *Bacillus anthracis* LeTx activate NLRP1 by PA & LF. *Listeria* and *Staphylococcus aureus* activate NLRP3 by bacterial pore-forming toxins, bacterial RNA, and bacterial cell wall components LPS. The endogenous bacteria and *Francisella* active NLRC4 and bacterial DNA sensor including AIM2, NLRP3, and NLRP1 inducing the cleavage of caspase-1 to release IL-1 $\beta$  and IL-18. Gram-negative bacterial LPS activate the non-classical inflammasome caspase-11. PA, protective antigen; LF: lethal factor; LPS, lipopolysaccharide; NLRP1, NACHT, LRR and PYD domains-containing protein 1; NLRC4, NLR family CARD domain-containing protein 4; NLRP3, NACHT, LRR and PYD domains-containing protein 3; AIM2, absent in melanoma 2; IL-1 $\beta$ , interleukin 1 beta; IL-18, interleukin 18.

biological processes, such as in embryonic formation and development, gene expression, and metabolism<sup>30</sup>. ncRNAs are also found to be associated with tumor triggering, development, progression and metastasis<sup>31</sup>, as well as diseases including diabetes, metabolic syndrome<sup>32</sup>, colitis<sup>33</sup>, autoimmunity<sup>34</sup> and neurodegeneration<sup>35</sup>. With the development of genomics and bioinformatics tools, especially the extensive application of high-throughput sequencing technology and single cell RNA sequencing (scRNA-Seq), increasing regulatory mechanisms of non-coding RNAs have been unfolded. Recently, ncRNAs, especially microRNAs, have been found implicated in the development of inflammatory responses and autophagy<sup>36</sup>, suggesting that the ncRNA is a potential precise target for treating autophagy-driven and inflammasome-associated diseases. For determining such a target, it is necessary to better explore the effects of ncRNAs on the interplay between autophagy and inflammasomes. Herein we are aimed at systematically analyzing the current understanding about the intersection of the role and mechanism among

autophagy, inflammasome and ncRNAs in infection and inflammatory diseases.

### Interaction between autophagy and inflammasome-mediated process

Researches in the crosstalk between autophagy and inflammasome activation are mostly known in pathological progression of bacterial infection (Fig. 2). Activation of the inflammasome and autophagy is critically important for host defenses against microbial invasion<sup>37</sup>. These two entities coordinate to enhance host defense and mammals are fortunate to have such a powerful pair of regulatory mechanisms to keep various diseases in check. However, the fact is that autophagy and inflammasome not only function in their own ways but also form complex interrelationship to exert an even stronger and critical impact in physiological and pathophysiological conditions. Although both inflammasome activation and autophagy play beneficial roles in host defense against infection, they do have



**Figure 2.** Interplay between autophagy and inflammasome activation during bacterial infection. Extracellular inject virulence factors into host cells via T3SS. Some of the virulence factors activate NLR4 mediated by NAIP proteins, and other virulence factors have strong destructive power to mitochondria. The damaged mitochondria release mtDNA, cardiolipin, ROS, and other activators of AIM2 and NLRP3. Then, AIM2, NLRP3, Caspase-11 and NLR4 combine with caspase-1 to form inflammasomes. Activated inflammasomes cleave proteins that are important for autophagy progress, such as ATG16L1, TRIF, and other receptor proteins, and trigger pyroptosis and liberate a number of inflammatory factors. However, activated autophagy during bacterial infection will attenuate pyroptosis and clear defective mitochondria which leads to the downregulation of such activators as mtDNA, cardiolipin, ROS, and  $\text{Ca}^{2+}$  of inflammasomes. Autophagy can also swallow pro-IL-18 and IL-1 $\beta$  which are necessary for mature inflammatory factors. NLR4, NLR family CARD domain-containing protein 4; NLRP3, NACHT, LRR and PYD domains-containing protein 3; AIM2, absent in melanoma 2; mtDNA, mitochondria DNA; ROS, Reactive oxygen species.

distinct and sometimes contrary effects. Inflammasome activation leads to inflammatory responses<sup>38</sup> and even results in cell death (pyroptosis), while autophagy tends to inhibit inflammation<sup>4</sup>. When autophagy is impaired in monocytes, IL-1 $\beta$  would be increased along with retention of dysfunctional mitochondria<sup>39</sup>. Importantly, autophagy down-regulates inflammasome activation by removing defective mitochondria (mitophagy)<sup>40</sup>. However, certain pathogens (e.g., *Salmonella*) can subvert host immune responses through hiding in autophagic vacuoles to avoid phagocytic clearance<sup>41</sup>. On the other hand, inflammasome components are also shown to regulate autophagy<sup>42</sup>. Furthermore, bacterial virulence factors or other induction factors may impact host response. The latest research in our lab also indicates that the CRISPR-Cas adaptive immune system may regulate host defense and alter inflammasome activation by augmenting autophagy<sup>43</sup>. Taken together, there is apparent complicate interaction between autophagy and the inflammasome-mediated process. Understanding the underlying mechanisms

may help create better weapons against bacterial infection.

A question follows naturally: which of these processes is more important, or the dominant, in the interaction between autophagy and inflammasome? Recent studies have uncovered that deletion of LC3B and Atg16L1, or depletion of Beclin1 along with introduction of an Atg4B dominant negative construct could apparently increase IL-1 $\beta$  secretion, showing that autophagy is an integral regulator of the inflammasome via regulation of ROS and autophagosomal degradation<sup>44,45</sup>. ROS, produced by NADPH oxidases in mitochondria in response to bacterial infection, requires pattern recognition receptors (PRR) such as TLRs, NLRs or lectins to activate inflammasomes<sup>46,47</sup>. One explanation is that inflammasomes are inhibited under autophagic condition<sup>48</sup>. In the deficiency of autophagy-related genes, such as *atg5*, *atg7*, *atg12*, and *atg16L1* (which are implicated in regulating endotoxin-induced inflammasome)<sup>49</sup>, autophagy does not function normally, resulting in accumulation of dysfunctional mitochondria and increased ROS release.

Inflammasomes in innate immune cells recognize ROS and produce proinflammatory cytokines<sup>50</sup>, while autophagy can reduce the accumulation of mitochondria by clearing the dysfunctional ones and peroxisomes, to slow down inflammatory responses. Collectively, these reports demonstrate that while ROS may enhance inflammation, it also activates autophagy to serve as a negative feedback during bacterial infection.

Moreover, inflammasomes are also regulated by autophagy through augmenting or decreasing IL-1 $\beta$  secretion, a determinant for inflammatory response<sup>51</sup>. Other evidence supports that ubiquitination of ASC is detectable upon absent in melanoma 2 (AIM2) stimulation regulatory proteins, which are able to stimulate autophagy in response to the invasion of bacteria<sup>52</sup>. A portion of ASC-containing inflammasomes are found to be redirected towards autophagosomes and autophagolysosomes upon NLRP3 or AIM2 activation<sup>53</sup>, indicating that autophagy often accompanies inflammasome activation. As discussed above, NLRs are cytoplasmic receptors that play a crucial role in the innate immune response by recognizing bacteria and initiating a fierce inflammatory reaction. These findings together indicate that balanced inflammatory responses are resulted from the NLRs controlling or coordinating autophagy<sup>47</sup>. Some bacteria are reported to involve interaction between inflammasome and autophagy (Table 1).

Crosstalk between autophagy and inflammasome activation is not limited to infections. Both autophagy and inflammasome are related to protein secretion, such as end-binding protein 1 (EB1)<sup>76</sup>, which seems to be a reciprocal mechanism. Furthermore, the dectin-1/Syk pathway activates unconventional, vesicle-mediated protein secretion that is dependent on both inflammasome complex assembly and autophagy activity in human macrophages<sup>77</sup>. TRIM20 (a subset of tripartite motif proteins) and TRIM21 were reported to directly bind with their respective cargo, leading to autophagic degradation. Further studies suggest that TRIM20 targets inflammasome components, such as NLRP3, NLRP1, and pro-caspase-1 for autophagic degradation, whereas TRIM21 targets IRF3<sup>78</sup>. In addition, autophagy is shown to regulate the secretion of proinflammatory cytokines through deletion of Atg16L1, an Atg5-Atg12 binding protein, which triggers the production and release of large amounts of inflammatory cytokines in response to LPS and other pathogen associated molecular patterns (PAMPs) of bacterial pathogens in mice. It will be interesting to understand more details of the interaction between autophagy and inflammasome modulation, as our knowledge in this interplay is only a tip of the iceberg.

### ncRNAs intermediating between inflammasomes and autophagy

miRNAs are small RNAs about 18-22 nucleotides and function at RNA silencing through base-pairing with

complementary sequences of three prime untranslated region (3'-UTR) or 5'-UTR of mRNA to regulate transcriptional gene expression<sup>79</sup>. For example, miRNA-223 was reported to target NLRP3 3'-UTR to suppress NLRP3 protein expression<sup>80,81</sup>, indicating that inflammasomes can be repressed by ncRNA (miRNA). Similarly, miRNAs are able to target the autophagy associated genes<sup>82</sup>, which highlights the double role of miRNAs in regulating both inflammasomes and autophagy. Tables 2 and 3 list the miRNAs and lncRNAs that are known to be involved in inflammasomes or autophagy machineries in different biological processes and their functional mechanisms. Except for miRNA103, all other miRNAs appear to regulate inflammasome and autophagy by targeting mRNA 3'-UTR of different genes. Among them, miR-301b and miR-302b were reportedly involved in *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* infection-induced inflammation, which may have potential link with inflammasome and require further investigation<sup>83</sup>. Likewise, a recent study reported that *P. aeruginosa* infection may be linked to inflammasomes<sup>84</sup> but its link with other miRNAs needs to be examined. Therefore, further studies are needed to find out the role of miRNAs and inflammasomes in other situations.

Similar to miRNAs, siRNA, a double-stranded RNA approximately 20-25 nt in length, interferes with the expression of genes by base-pairing with complementary sequences to degrade mRNA after transcription<sup>85</sup>. siRNA has been an indispensable tool for manipulating gene expression in wide-spread scopes of experimental studies including research involving inflammasome and autophagy.

Different from miRNAs and siRNAs, circRNAs do not have 5' or 3' ends and usually function as a sponge of miRNAs<sup>86</sup>. Thus far, although only a small portion of circRNAs, such as circRNA mm9, circRNA CBT15, circ005915 and circR1011, are reportedly associated with NLRP3 inflammasome activation after PM<sub>2.5</sub> treatment<sup>87</sup>, circRNAs are speculated to contribute to inflammasome activation in other potential biological processes. Also notable is that circPAN3<sup>88</sup>, circHIPK3<sup>89</sup>, circ104075<sup>90</sup>, circHECTD1<sup>91</sup>, circRNA.2837<sup>92</sup>, circ0001946<sup>93</sup>, ciR-012091<sup>94</sup>, circNRIP1<sup>95</sup> and circACR<sup>96</sup> were found to regulate autophagy by targeting autophagy-associated miRNAs, implying that autophagy is strongly impacted by the circRNA-miRNA axis. However, there might be other mechanisms with small ncRNAs in coordinating inflammasome assembly and autophagy machinery, requiring further investigations.

As a sponge of miRNAs, lncRNAs have been increasingly recognized for important function in a variety of cellular activities in recent years. Though lncRNAs are acknowledged to be linked to the autophagy process, only limited literature showed their direct association with inflammasomes. However, studies did indicate that lncRNAs were involved in inflammation and immune diseases<sup>97</sup>. We summarized recent researches that reported the association of lncRNAs with inflam-

**Table 1.** Microbes activate inflammasome and autophagy.

Microbe	Adaptation in inflammasome	Adaptation in autophagy.	Ref
<i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i> can inhibit the expression of IL-1 $\beta$ through metalloproteinase being encoded by <i>zmp1</i> gene.	IL-4 and IL-13 inhibit IFN $\gamma$ or starvation-induced autophagic elimination of <i>M. tuberculosis</i> .	[54] [55]
<i>P. aeruginosa</i>	<i>P. aeruginosa</i> import effector protein ExoU and restrain the activation of caspase-1 and IL-1 $\beta$ .	Caspase-1 cleavage of TRIF thus inhibits autophagy and $\beta$ -interferon production during <i>P. aeruginosa</i> infection.	[56] [57]
<i>Bacillus anthracis</i>	<i>Bacillus anthracis</i> lethal toxin induced activation of caspase-1 was able to attenuate proIL-1 $\beta$ due to the cell death and the activation of the caspase-1.	Autophagy induction may protect cells against anthrax lethal toxin.	[58] [59]
<i>Mycobacterium marinum</i>	<i>M. marinum</i> secretion system ESX-1 plays an important role in the process of escaping from the host cell's phagocytosis.	<i>M. marinum</i> are escorted by a distinct polar autophagocytic vacuole. Cell-to-cell transmission is inhibited once autophagy is impaired and the host cells die.	[60] [61]
<i>Yersinia pseudotuberculosis</i>	Effector molecules YopK and T3SS interact and inhibit host recognition of T3SS and activation of inflammasome. YopK defects can enhance the activity of inflammasome and host bacterial clearance.	Cells showed significant cytoplasmic localization of p53 and reduced LC3-I to LC3-II conversion responding to <i>Yersinia pseudotuberculosis</i> infection	[62] [63]
<i>Staphylococcus aureus</i>	IL-1 $\beta$ produced by the activation of inflammatory cells can promote chemotaxis of neutrophils and bacterial clearance.	Atg5 deficiency inhibits bacterial degradation in autolysosomes.	[64] [65]
<i>Shigella flexneri</i>	<i>Shigella flexneri</i> concerters modulation of pro-death and pro-survival signaling pathways to circumvent the innate immune response.	IcsB and VirA act synergistically at vicinity of the vacuole membrane to allow <i>Shigella flexneri</i> to escape from LC3-positive vacuoles.	[66] [67]
<i>Listeria monocytogenes</i>	Inflammasome-mediated inhibition of <i>Listeria monocytogenes</i> -stimulated immunity is important for bacterial accumulation in CD8 $\alpha$ (+) DCs.	<i>L. monocytogenes</i> prevents phagosomes forming.	[68] [69]
<i>Porphyromonas gingivalis</i> (Pg)	<i>P. gingivalis</i> reduces IL-1 $\beta$ secretion and escapes host immune response, owing to <i>P. gingivalis</i> and Pg-LPS differentially controlled the NLRP3 inflammasome pathway in endothelial cells.	The bacteria evade endocytic trafficking to lysosomes by trafficking to autophagosomes.	[70] [71]
<i>Legionella pneumophila</i>	<i>L. pneumophila</i> may have encountered little selective pressure to evade PRRs recognition and immune responses.	<i>L. pneumophila</i> replication vacuoles have autophagy markers. It is postulated that the bacterium delays autophagosome maturation early after infection.	[72] [73]
<i>Burkholderia pseudomallei</i>	The specific mutants of <i>B. pseudomallei</i> eg. <i>sifA</i> and <i>sdhA</i> , aberrantly enter the cytosol and trigger caspase-11 protects against bacteria that escape the vacuole.	<i>B. pseudomallei</i> prevents bacterial colocalization with LC3 autophagosome marker.	[74] [75]

masome (Table 2) and autophagy (Table 3). Among them, lncRNA-MEG3 is the only lncRNA confirmed to regulate autophagy during bacterium (*P. aeruginosa* and *Mycobacteria*) infection<sup>98,99</sup>, while others predominantly linked to cancers (Table 3). These studies provide a novel perspective to further explore ncRNAs in regulating inflammasomes and autophagy. Nevertheless, it is currently unclear whether lncRNAs can link with inflammasome activation and autophagy processes at the same time. Until 2017 when Meng et al. found the shRNA disturbance of NLRP3 inflammasome through autophagy activation in alleviating ischemia reperfusion-induced damage<sup>100</sup>, which is a critical example to link the ncRNA, inflammasome, and autophagy together. Then in 2018, Xue et al. confirmed that Cox2 (lincRNA) interferes with NLRP3 inflammasome- and autophagy-mediated inflammation. Mechanistically, these authors delineated that Cox2 promotes the NF- $\kappa$ B p65 nuclear translocation by directly binding to p65, leading to increased IL-1 $\beta$

secretion. Meanwhile, Cox2 regulates the expression of NLRP3 and ASC, which further promotes the IL-1 $\beta$  secretion. The increased IL-1 $\beta$  then enhances the TIR-domain-containing adapter-inducing interferon- $\beta$  (TRIF) cleavage. Hence, the TRIF-mediated autophagy is inhibited<sup>101</sup>. These studies elucidate the links between ncRNAs and inflammasome-autophagy crosstalk and highlight the necessity to further delve into more links and the underlying mechanisms.

### Links of autophagy, inflammasomes, and ncRNAs to human diseases

Inflammasome activation are critical for host immunity against pathogens, so their disturbance is closely related to the occurrence and development of various human diseases. In addition to bacterial infection and immunity, Type 2 diabetes is also found to be associated with the NLRP3 inflammasome<sup>102,103</sup>. The primary causes of Type 2

**Table 2.** Crosstalk of ncRNAs and inflammasomes.

ncRNAs	Function	Interaction	Ref
microRNA7	Controlling mRNA expression	NLRP3 as a target gene of miR-7	[132]
microRNA155	Roles in physiological and pathological processes	Increasing inflammasome-associated gene expression	[133]
microRNA377	A biomarker of oxidative stress	Activating O2(-)/p38 MAPK/TXNIP/NLRP3 inflammasome pathway when overexpressed	[134]
microRNA223	Regulating expression levels of other genes	Binding to NLRP3 3'-UTR sites	[80]
microRNA143	Regulating expression levels of other genes	miR-143 increasing the expression of AIM2 and ASC mRNAs	[135]
microRNA20a	Controlling mRNA expression	Regulating expression of NLRP3 by targeting TXNIP	[136]
microRNA133a-1	Regulating expression levels of other genes	Suppressing inflammasome activation through UCP2	[137]
microRNABART15	Epstein-Barr virus miRNA	Targeting NLRP3 3'-UTR	[138]
microRNA9	Inhibiting target mRNAs by binding to their 3'-UTRs	Targeting ELAVL1 to inhibit pyroptosis	[139]
microRNA21	Inhibiting phosphatases	Activating NLRP3 in liver fibrosis	[140]
microRNA92a	Inhibiting endothelial cell angiogenesis	SREBP2-miR-92a-inflammasome responding to oxidative stress	[141]
microRNA146a	Anti-inflammatory microRNA	Upregulating inflammasome gene activation in diabetic nephropathy	[142]
microRNA-30c-5	Regulating expression levels of other genes	Inhibiting NLRP3 inflammasome in atherosclerosis	[143]
microRNA-495	A tumor-suppressor	Suppressing NLRP3 signaling pathway in endothelial cell injury	[144]
miR-186	Controlling mRNA expression	Suppressing NLRP3 signaling to control neuropathic pain	[75]
lncRNA XIST	Involved in cell proliferation migration, inflammation process and apoptosis	Inhibiting bacteria induced production of NLRP3 inflammasome	[76]
lncRNA ANRIL	Participating in NF- $\kappa$ B-mediated signaling	Increasing NLRP3 activation in nephropathy	[77]
lncRNA SNHG1	A competing endogenous RNA	Regulating NLRP3 Pathway in parkinson's disease	[78]
lncRNA Neat1	Regulating biological processes	Increasing activation of inflammasomes in innate immunity	[145]

diabetes are insulin resistance and functional deficiency of pancreatic beta cells. Long-term high glucose concentration stimulates the islet cells to activate NLRP3 and trigger inflammation and compound the dysfunction of pancreatic beta cells, ultimately leading to development of Type 2 diabetes<sup>104</sup>. The damage of mitochondria apparatus is also closely associated with insulin resistance and functional damage of pancreatic beta cells, due to its critical energy generating function<sup>105</sup>. It is not surprising that autophagy process as a cell self-protection mechanism plays a vital role in maintaining the structure and function of pancreatic beta cells and in improving insulin resistance. However, the present understanding about the link between autophagy and diabetes is still preliminary, and further investigation is needed to provide insight into the mechanisms of the disease etiology and to offer improved treatments.

The NLRP3 inflammasome is also found to be linked with the occurrence of nonalcoholic fatty liver, by its high expression in the model of nonalcoholic fatty liver in mice<sup>106</sup>. Another study found that the long-time high fat intake caused the decline of mitochondrial autophagy level and mitochondrial breakdown, which in turn were associated with an impaired mitophagy to aggravate liver NLRP3 inflammasome activation in a murine nonalcoholic steatohepatitis model<sup>107</sup>. Again, these studies confirmed that normal level autophagy is vital to maintain cell metabolism in the liver and

keep the liver functioning properly. Numerous studies have also demonstrated dysfunctional autophagy levels in a variety of liver diseases caused by alcohol, drugs, viral hepatitis, and ischemia-reperfusion injury<sup>108</sup>. These results show the important effect of autophagy on the complex assembly of inflammasomes in liver disorders. With further understanding of the role of autophagy in liver diseases, it may be possible to treat liver diseases by rescuing autophagy.

Inflammasome activation also triggers cardiovascular and cerebrovascular diseases and acute interstitial renal injury<sup>109</sup>. A major factor of hypertension pathophysiology is the NLRP3-associated inflammation<sup>110</sup>, while NF- $\kappa$ B, the effective activator of NLRP3 was reported to be suppressed by the activation of AMPK in the hypertension process<sup>111</sup>. Peng et al. found that P2X7R contributes to the progression of atherosclerosis by promoting NLRP3 inflammasome activation<sup>112</sup>, whereas Sirt6 was reported to stabilize atherosclerosis plaques by promoting autophagy<sup>113</sup>. These studies illustrate that autophagy may be involved in the energy consumption mechanisms to adjust metabolism and maintain homeostasis, and that altering the delicate regulation of these processes will impose tissue injury and cause serious organ dysfunction and disease development.

In inflammatory diseases, inflammasome was found to have a beneficial role in inflammatory bowel disease

**Table 3.** Crosstalk of ncRNAs and autophagy.

ncRNAs	Function	Interaction	Ref
microRNA24-3p	Regulating gene expression	Suppressing DEDD transcription	[146]
microRNA539	Regulating gene expression	Targeting the 3'-UTR of mek which suppressed autophagy in H9C2 cells	[147]
antimicroRNA30b	Targeting 3'-UTR of genes	miR-30b represses autophagy then promotes TNF- $\alpha$ -induced apoptosis	[148]
microRNA221	Targeting tumor suppressors	Targeting the autophagy gene <i>beclin-1</i> in tumor cell death	[149]
microRNA27a	A brain-specific miRNA	Binding to FoxO3a mRNA which regulates autophagy	[150]
microRNA199a-5p	Regulating gene expression	Inhibiting cisplatin-induced drug resistance by inhibiting of autophagy process	[151]
microRNA128	A brain-enriched miRNA involved in gene expression regulating	Repressing mTOR signaling that regulates cytotoxicity	[152]
microRNA103/107	One of the only known miRNA which can target 5'-UTR	Preserving end-stage of autophagy via regulating diacylglycerol kinase C signal pathway	[153]
microRNA99	Antiviral miRNA	Increasing autophagy during hepatitis B virus infection	[154]
microRNA146a	A mediator of inflammation	Repressing Bcl-2 and promoting autophagy in Hypoxia condition	[155]
microRNA20a	Regulating gene expression	Targeting ATG7 and ATG16L1 in macrophage cells	[156]
microRNA21	Regulating gene expression	Inhibiting autophagy via PTEN/Akt/HIF-1 $\alpha$ and Akt-mTOR pathways	[157]
microRNA34a	Regulating gene expression	Mediating SIRT1/mTOR autophagy pathway	[158]
microRNA23a	Regulating the expressions of other genes	Repressing autophagy in premature senescence	[159]
microRNA144*	Regulating the expression of genes involved in erythropoiesis and other process	Targeting the autophagy protein DRAM2 during <i>Mycobacterium tuberculosis</i> infection.	[160]
microRNA195	Affecting stability and translation of mRNAs	Targeting GABARAPL1 which is a upstream regulator of autophagy under hypoxic conditions	[161]
microRNA222	A known extracellular RNA	Inhibiting autophagy after cardiac-specific overexpression	[162]
microRNA140-5p	A miRNA signature of kinds tumors	Regulating IP3k2 induced drug resistance by inducing autophagy in osteosarcoma cells	[163]
microRNA22	Binding to the 3'-UTR of other mRNAs	Targeting p38 $\alpha$ to regulate regulates starvation-induced	[164]
microRNA124-3p	Neuronal cell associated miR	Inhibiting autophagy gene <i>beclin-1</i> in breast cancer cell	[165]
microRNA30a-3p	Highly expressed in heart cells	Targeting BECN1 to regulate autophagy during <i>L. donovani</i> infection	[166]
microRNAlet-7 g	Regulating gene expression	Regulating autophagy by rapamycin signaling in granulosa cells	[167]
microRNA153	Regulating gene expression	Regulating autophagy through targeting Mcl-1 in cardiomyocytes	[168]
microRNA384-5p	Mainly functioning in neural system.	Targeting Beclin-1 to regulate autophagy in macrophage cell	[169]
microRNA965	Shrimp miR	Targeting the autophagy gene ATG5 against virus infection	[170]
microRNA126	Regulating gene expression	Alerting cell metabolism to induce autophagy in malignant mesothelioma	[171]
microRNA19a-39/19b-3p	Oxidative stress associated miR	Targeting TGF-beta1 to inhibit autophagy	[172]
microRNA33	Strongly associated with lipid metabolism	Reprogramming autophagy induced by <i>Mycobacterium tuberculosis</i>	[173]
microRNA299-5p	Regulating gene expression	Targeting autophagy gene <i>atg5</i> to control apoptosis	[174]
microRNA141	Regulating gene expression	Targeting HMGB1 to regulate autophagy	[175]
microRNA181a-5p	A miR involved in multiple processes	Repressing autophagy in during detachment induction	[176]
microRNA376	Important for cancer formation	Regulating macroautophagy	[177]
microRNA26b	Playing roles in hypoxia, neuronal differentiation, hepatocellular carcinoma, etc.	Targeting ULK2 to inhibit autophagy in cancer cells	[178]
microRNA495	Regulating gene expression	Targeting autophagy gene <i>atg3</i> during starvation	[179]
microRNA1273g-3p	Mainly involved in HIF-1 signaling pathway and the nervous system	Regulating glucose fluctuation-induced autophagy	[180]
microRNA301a/b	Regulating gene expression	Increasing cell autophagy in hypoxia condition	[181]
microRNA142a-5p	Targeting 3'-UTR of mRNAs	Regulating beclin-1-mediated autophagy after LPS-Induced	[182]

Table 3. Continued.

ncRNAs	Function	Interaction	Ref
microRNA1303	Regulating gene expression	Targeting autophagy gene <i>atg2b</i> during bacterial infection	[183]
microRNA129-5p	Regulating gene expression	Targeting HMGB1 in breast cancer	[184]
microRNA183	Regulating gene expression	Targeting UVRAG, a regulator of autophagy and apoptosis in colorectal cancer	[185]
microRNA96	Targeting 3'-UTR of genes	Targeting MTOR or ATG7 respectively at different expression levels	[186]
microRNALET7I	Regulating gene expression	Increasing autophagy via targeting IGF1R to protect T cell from death	[187]
microRNA451	Regulating gene expression	Targeting TSC1 to regulate autophagy	[188]
microRNA204-5P	Cancer associated miR	Inhibiting activity of LC3B-II	[189]
microRNA200C	Mainly associated with cancer	Targeting UBQLN1 to inhibit autophagy in breast cancer cells	[190]
microRNA17-5p	Regulating gene expression	Targets Mcl-1 and STAT3 to active autophagy in macrophages after mycobacterium tuberculosis infection	[191]
microRNA212	Regulating gene expression	Inhibiting starvation induced autophagy in cancer cells by targeting SIRT1	[192]
microRNA14-3p	Mainly involved in cardiac morphogenesis and cancer	Targeting GABARAPL1 which inhibits autophagy in gastric cancer cells	[193]
microRNA497	Regulating gene expression	Repressing autophagy in reoxygenation injury in cardiomyocytes	[194]
microRNA23b-3p	Mainly involved in cancer	Targeting autophagy genes <i>atg12</i> and <i>hmg2</i> in gastric cancer cells	[195]
microRNA125a	Mainly involved in monocytes during mycobacterium infection	Blocking <i>M. tuberculosis</i> -induced autophagy	[196]
microRNA188-3p	Inducing autophagic cell death in cancer cells	Targeted by lncRNA APF and targeting <i>atg7</i>	[197]
microRNA423-5p	Regulating gene expression.	Increasing autophagy activity in hepatocellular carcinoma	[198]
microRNA638	Regulating gene expression	Targeting TFAP2A/AP-2 $\alpha$ and regulating autophagy in melanoma cells	[199]
microRNA214	Associated with various cancers with functions varying in different tissues	Targets UCP2 to promote autophagy in breast cancers	[200]
microRNA20a	Hypoxia sensitive miR	Targeting autophagy gens ATG5/FIP200 in colorectal cancer	[164]
lncRNAHotair	Playing roles in myeloid transcriptional regulation	HOTAIRM1 acting as a miR-20a/106b sponge to regulate autophagy pathway	[201]
lncRNAH19	Involved in diabetic cardiomyopathy	H19 inhibiting autophagy activation by promoting mTOR phosphorylation in cardiomyocytes	[202]
lncRNA HNF1A-AS1	Involved in carcinogenesis and cancer	Regulating autophagy by miR-30b which can target Bcl-2	[203]
lncRNAMALAT1	Transcript 1 of metastasis-associated lung adenocarcinoma	Promoting autophagy activation in aggressive pancreatic cancer	[204]
lncRNANBR2	Regulating diverse biological processes	LKB1-AMPK- NBR2 feedback loop under energy stress	[205]
lncRNA TINCR	Mainly sponging miRs	Sp3 binding to TINCR promoters and promoting autophagy in cutaneous squamous cell carcinoma	[206]
lncRNA CA7-4	Mainly sponging miRs	Promoting autophagy by sponging MIR877-3P and MIR5680 in endothelial cells	[207]
lncRNA17A	Involved in neurodegenerative disorders	Promoting autophagy in Alzheimer's disease model	[208]
lncRNA OGF1P1	Regulating diverse biological processes	Inhibiting autophagy through AKT/mTOR signaling in coronary artery endothelial cells	[209]
lncRNA BLACAT1	Mainly sponging miRs	Promoting autophagy gene <i>atg7</i> expression via miR-17 in lung cancer	[210]
lncRNA MEG3	Involved in cancer and bacterial infection	Promoting autophagy in glioma and during bacterial infection	[211] [99]

(IBD), showing that NLRP3 inflammasome activation helps maintain the intestinal microbial balance of flora and suppresses colitis-associated tumors. Furthermore, other NLR family proteins including

NLRC4, NLRP6, and NLRP3 may also play a role in colitis<sup>114</sup>.

As the central link in inflammation, inflammasomes may be involved in genetic diseases, such as Webster's

syndrome, whose gene mutation may over-activate NLRP3 inflammasomes, resulting in excessive production of pro-inflammatory factors<sup>115</sup>. The existing data showed that one of the factors in the development of acute lung injury is the dysregulated inflammatory responses<sup>116</sup>. Moreover, studies have shown that the serum levels of IL-1 $\beta$  and IL-18 in cancer patients are positively correlated with the malignancy of tumors and negatively correlated with the survival rate of patients, revealing the close association between inflammasomes and tumors<sup>117</sup>. lncRNA GAS5 was found to suppress ovarian cancer by inducing inflammasome formation<sup>118</sup>. In summary, inflammasome activation is involved in genetic diseases, chronic inflammatory diseases, cancer, besides others.

Like inflammasome, autophagy is also involved with nervous system diseases and cardiovascular diseases (cardiomyopathy, cardiac hypertrophy, ischemic heart disease, and heart failure). In the brain of patients with Alzheimer's disease (AD), accelerated accumulation of autophagosomes and Alzheimer's amyloid plaques activate the NLRP3 inflammasome<sup>119</sup>. Undoubtedly, regulatory ncRNAs are also tightly associated with diseases, such as cancer, nervous system diseases, and heart disease. Many lncRNAs are shown to be associated with breast cancer. As an example, the aberrant expression of lncRNAs that regulate the telomerase TERT gene in breast cancer cells (including precancerous cells) may increase telomerase activity, thereby enhancing cancer cell growth and inhibiting apoptosis<sup>120</sup>. The cardiovascular system has a particularly rich source of miRNAs, which play diverse roles in cardiovascular diseases. Certain miRNAs may be attributed to the potential susceptibility of the heart and blood vessels to injury, while other miRNAs may help sustain cardiovascular function and homeostasis<sup>121</sup>. The roles of ncRNA in inflammasome activation- or autophagy-related diseases only began to be unfolded and are worth further studying. For example, miR-30A was the first small noncoding RNA identified as an autophagy regulator by targeting the *beclin1* gene in a spectrum of cancer cells<sup>122</sup>. Altogether, we have just briefly touched the base of these complex intertwined regulatory pathways, and it is almost impossible to build a complete hierarchy map. Nevertheless, typical examples have already demonstrated the important interplay between inflammasome, autophagy, and ncRNA in human diseases. We here provide some online resource links (<http://www.cuilab.cn/lncrnadisease> for lncRNA and <http://www.cuilab.cn/hmdd> for microRNA).

### Targeting ncRNAs to treat diseases involving autophagy and inflammasomes

Although RNA drugs have been extensively designed and developed for 30 years, only a handful of RNA-based small molecule drugs are currently on the market

worldwide, such as Exondys 51 (for Duchenne Muscular Dystrophy)<sup>123</sup>, Macugen (for vascular disease)<sup>124</sup>, Vit-ravene (for cytomegalovirus disease)<sup>125</sup>, Kynamro (for familial hypercholesterolemia)<sup>126</sup>, Defitelio (for veno-occlusive disease)<sup>127</sup>, and Spinraza (for muscular atrophy)<sup>128</sup>. Recently, Dr. Matt Disney of the Scripps Research Institute in Florida, has discovered a small molecule called targaprimir-96 that binds to a precursor of miRNA-96, pri-miR-96. Pri-miR-96 generates mir-96 through RNA mutation, which is a carcinogenic miRNA, and can reduce the activity of FOXO1 to perform an important role in triggering breast cancer<sup>129</sup>. However, there is still a long way before making it a clinical drug. Chemist Amanda Hargrove's team at Duke University analyzed the chemical informatics of ligands for 100 targeted RNAs and found that the same library of compounds used to target proteins could also be used for targeting RNAs, meaning lower risk for humans due to their solubility, permeability and toxicity<sup>130</sup>. We believe that as screening technology fast advances, RNAs targeted drug research would be more feasible and eventually enter the clinic. Another way to target ncRNAs is interrupting the regulation between them. For example, lncRNA TGF $\beta$ 2-OT1 can regulate miRNAs in autophagy and inflammation of vascular endothelial cells<sup>131</sup>. If the interactions between lncRNAs and miRNAs were prevented, the subsequent cascade of reactions would be terminated.

### Summary and perspective

The fundamental understanding of the crosstalk between inflammasome activation and autophagy will add to the design of therapeutics for various diseases, such as chronic inflammatory and drug resistance in infection and cancer. Recent research sheds light on the molecular complexity of autophagy and inflammasome activation under bacterial infection, which may be harnessed to control drug resistance to infection. With the development of new technologies like CRISPR-Cas enabling the easy editing of autophagy factors and inflammasome machineries for improving knowledge in this field, more insight will be illuminated with the continued research.

In the three-party interplay, ncRNAs will have a big impact on disease through intermediating between autophagy and inflammasome. We know that more than half of the eukaryote DNA are transcribed into RNA, most of which are ncRNAs. Accumulating evidence suggests that ncRNAs play important roles in biological processes including development, physiologic functions, metabolism, and disease. However, unlike the mechanism about autophagy and inflammasomes, much less is known about how ncRNAs regulate these processes in each of the many conditions: where the ncRNAs are from; where they go to; what/how they function; or even whether each or most of them have an important biological significance. Thanks to the high-throughput

screening technologies, for example next-generation sequencing (NGS) and scRNA-Seq, characterization of ncRNA would be unprecedentedly faster. It is clear that ncRNAs have a wide range of functions. The main task in the near future is to discover their functional roles and potential links to diseases, which will be truly time-consuming and full of difficulty. It is hoped that a thorough understanding of the regulatory network of ncRNAs, inflammasomes and autophagy will provide the breakthrough in the demystification of the function of the interactome. ncRNAs-based therapeutics or regulators for inflammasome or autophagy may add to the treatments to enhance efficacy and reduce side effects, representing the exciting, revolutionary feature of precision medicine.

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## Conflict of interest

The authors declare no conflict of interest.

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